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Does conversion affect short-term and oncologic outcomes after laparoscopy for colorectal cancer?

Marco Ettore Allaix[1] , Maurizio Degiuli[1], Alberto Arezzo[1], Simone Arolfo[1] and Mario Morino[1]
(1)
Department of Surgical Sciences, University of Turin, Corso A. M. Dogliotti 14, 10126 Turin, Italy

Marco Ettore Allaix
Email: meallaix@gmail.com

Mario Morino (Corresponding author)
Email: mario.morino@unito.it

Abstract
Background
Conversion of laparoscopic colorectal resection (LCR) for cancer has been associated with adverse short-term and oncologic outcomes. However, most studies have had small sample sizes and short follow-up periods. This study aimed to evaluate the impact of conversion to open surgery on early postoperative outcomes and survival among patients undergoing LCR for nonmetastatic colorectal cancer.
Methods
A prospective database of consecutive LCRs for nonmetastatic colorectal cancer was reviewed. Patients who required conversion (CONV group) were compared with those who had completed laparoscopic resection (LAP group). Only patients with a minimum 5-year follow-up period were included in the oncologic analysis. Kaplan–Meier curves were compared to analyze survival. A multivariate analysis was performed to identify predictors of poor survival.
Results
The conversion rate was 10.9 %. The most common reason for conversion was a locally advanced tumor (48.4 %). Conversion was associated with a significantly longer operative time and a greater blood loss. No differences were observed in terms of postoperative morbidity, mortality, or hospital stay between the CONV and LAP patients. During a median follow-up period of 120 months (range, 60–180 months), the CONV group had a significantly worse 5-year overall survival (OS) (79.4 vs 87.4 %; p = 0.016) and disease-free survival (DFS) (65.4 vs 79.6 %; p = 0.013). Univariate analysis showed that conversion to open surgery, postoperative complications, anastomotic leakage, pT4 cancer, stage 3 disease, and adjuvant chemotherapy were significant risk factors for OS and DFS. On multivariate analysis, pT4 cancer and a lymph node ratio (LNR) of 0.25 or greater were the only independent predictors of DFS and OS, whereas a LNR of 0.01 to 0.24 showed a trend that did not reach statistical significance.
Conclusion
Conversion to open surgery per se is not associated with worse early postoperative outcomes and does not adversely affect long-term survival per se.
Keywords
Conversion Laparoscopy Morbidity Survival Recurrence Colorectal cancer

Large multicenter randomized clinical trials (RCTs) [*1*–*4*] have shown several short-term benefits of laparoscopic resection compared with open resection for colon cancer, such as reduced intraoperative blood loss, postoperative pain, and morbidity; improved postoperative pulmonary function; and shorter duration of postoperative ileus, translating into a shorter hospital stay and reduced costs.

Recent large RCTs [5, 6] as well as a systematic review and metaanalysis of the literature [7] have reported similar advantages of laparoscopic rectal resection and total mesorectal excision (TME) compared with open surgery for extraperitoneal rectal cancer.
Evidence from the literature also has shown comparable outcomes in terms of oncologic clearance and long-term survival between laparoscopic and open resection for colon [1, 8–10] and rectal cancer [10–12].
The rates for conversion of laparoscopic colon resection to open surgery reported in the largest multicenter RCTs range from 17 to 25 % [2–4], whereas the conversion rates for laparoscopic rectal resection vary between 0.6 and 32.4 % [7]. With the exception of the conventional versus laparoscopic-associated surgery in colorectal cancer (CLASICC) trial, all RCTs have analyzed converted patients in the laparoscopic group on an “intention-to-treat” basis.
A few nonrandomized studies have examined the short-term outcomes for converted cancer patients. Some studies have reported higher morbidity and mortality rates and a longer postoperative hospital stay [3, 13–18], whereas others did not find significant differences in comparisons with to non converted patients [12, 19–22]. The oncologic outcomes for converted patients are poorly investigated, and the data currently available are unclear [10, 12–23].
This study aimed to evaluate the impact of conversion to open surgery on short- and long-term outcomes in a large series of patients undergoing laparoscopic resection for nonmetastatic colorectal cancer.

Materials and methods

This study was a retrospective analysis of a prospectively collected database. Consecutive patients with colorectal cancer referred for surgical management at our Institution between January 1993 and December 2012 and treated laparoscopically were identified.
The exclusion criteria were preoperative diagnosis of liver or lung metastases or peritoneal carcinomatosis, invasion of adjacent organs evident preoperatively, acute intestinal obstruction or perforation, and history of colorectal surgery.
All the procedures were performed by two surgeons (M.M., M.D.) who had extensive experience in colorectal and laparoscopic advanced surgery using the same oncologic principles in all procedures (i.e., adequate margins of resection, en bloc vascular resection and lymphadenectomy, and minimal intraoperative manipulation of the tumor).
During right hemicolectomy, the bowel specimen was extracted through a transverse incision using of a wound protector, and an extracorporeal end-to-end hand-sewn or side-to-side stapled anastomosis was performed. During left hemicolectomy, sigmoidectomy, and anterior resection, the specimen was removed through a small suprapubic transverse incision, and the anastomosis was performed by laparoscopic transanal intracorporeal stapled technique. A partial mesorectal excision was performed for the treatment of upper rectal cancers, whereas a TME was performed in cases of mid-lower rectal cancers. When digital examination showed tumor involvement of the anatomic anal canal or tumor fixation to the pelvic floor, a laparoscopic abdominoperineal resection (APR) was performed.
The preoperative workup was standardized for both the colon and rectal cancer patients. The evaluation of the colon cancer patients included physical examination, total colonoscopy, abdominal computed tomography (CT) scan, chest X-ray, and carcinoembryonic antigen (CEA) assay.
The preoperative staging of rectal cancer included chest and upper abdominal CT scan and transanal endoscopic ultrasound. A pelvic CT scan was obtained until 2003, after which all patients underwent pelvic magnetic resonance imaging (MRI).
Neoadjuvant chemoradiotherapy (CRT) for extraperitoneal rectal cancer patients was discussed in a multidisciplinary setting. Patients preoperatively staged as T3–T4 N0–N1 without distant metastases received preoperative CRT (45 Gy over 4 weeks, together with systemic 5-fluouracil

intravenous infusion) and were reevaluated with clinical examination, rigid rectoscopy, endoscopic ultrasound, and CT or MRI 4 weeks after completion of the CRT. The definitive indication for laparoscopic TME was decided at this point, excluding T4 tumors that did not show clinical downstaging or downsizing because they were considered a contraindication to the laparoscopic approach.

The pre- and postoperative management was standardized. Preoperative mechanical bowel preparation was routinely used until 2005. In all cases, intravenous antibiotic prophylaxis was administered before incision. Unless contraindicated, antithrombotic prophylaxis with subcutaneous heparin and a sequential compression device was routinely used. Postoperative analgesia was achieved by intravenous local anesthetics (such as bupivacaine) for the first 48 h and by paracetamol and parenteral nonsteroidal analgesics. Oral intake was allowed the day after the first flatus occurred.

A prospective protocol was designed to evaluate the following parameters: patient's characteristics (age, gender, and American Society of Anesthesiologists [ASA] score), indications for surgery, operative variables, pathologic examination, short-term (within 30 days after surgery), and long-term oncologic outcomes. The operative variables included operative time (from skin incision to the application of dressings), intraoperative morbidity, mortality, and rate of conversion to open surgery. Conversion to open surgery was defined as an unplanned incision or an incision made larger or earlier than planned. The short-term outcomes included resumption of gastrointestinal functions, morbidity according to Dindo classification [*24*], and length of postoperative hospital stay.

Pathologic examination included stage of disease according to the tumor node metastasis (TNM) classification [*25*], length of the surgical specimen, number of lymph nodes harvested, lymph node ratio (LNR) (defined as the number of positive nodes divided by the total nodes harvested), and resection margins (longitudinal and radial in case of rectal cancer). Lymph nodes in the mesocolonic and mesorectal fatty tissue were identified after formalin fixation of the specimen. Stage 3 patients were divided into two categories according to LNR (0.01–0.24 and ≥0.25).

Only patients undergoing laparoscopic colorectal resection (LCR) by 31 December 2007 were included in the long-term oncologic analysis. Adjuvant chemotherapy was administered routinely to stages 2 and 3 colon cancer patients. Similarly, all rectal cancer patients undergoing neoadjuvant CRT and those with a postoperative diagnosis of stage 2 or 3 cancer were offered an adjuvant treatment after a clinical oncologic evaluation within 8 weeks after surgery.

All colon cancer patients were followed up with clinical examination, serum CEA assay every 3 months, and liver ultrasound every 6 months for the first 2 years, then annually. Chest X-ray and a CT scan of the abdomen and pelvis were performed every year. A colonoscopy was performed at 12 months, then every 3 years.

The follow-up assessment of rectal cancer patients consisted of digital examination, rectoscopy, and CEA assay every 3 months for the first 2 years, then every 6 months. A full colonoscopy was performed at 12 months and then every 3 years. A chest CT scan and a CT scan of the abdomen and pelvis were obtained at 6 and 12 months, then every year thereafter.

The long-term oncologic outcomes included the local recurrence rate, the incidence of abdominal wall and distant metastases, overall survival (OS), and disease-free survival (DFS). The data were collected prospectively from the time the primary malignancy was diagnosed.

Statistical analysis

Quantitative data are given as median and range, and categorical data are expressed as percentages. Proportions were compared using the chi-square test or Fisher's exact test, where appropriate. Student's t test was used to compare normally distributed variables. Patients with a minimum follow-up period of 60 months were included in the oncologic analysis.

Univariate analyses of 5-year OS and DFS rates were performed using the Kaplan–Meier method, and the differences between the groups were analyzed using the log-rank test. Patients' observations were censored on the date of last examination or death.
A multivariable Cox regression analysis was performed to identify predictive factors of poor DFS and OS using both forward and backward stepwise selection. Explanatory variables with univariable p values equal to 0.200 or lower were included in the multivariable analysis. This significance level was chosen to incorporate all potentially important predictor variables in the final modeling process. The variables analyzed were age, gender, tumor site, conversion to open surgery, pT staging, number of harvested lymph nodes, LNR, perioperative blood transfusion, postoperative complications, postoperative anastomotic leakage, and adjuvant chemotherapy. The results are reported as hazard ratios (HR) with 95 % confidence intervals (CI). A level of 5 % was set as the criterion for statistical significance. The data were collected on an Excel spreadsheet. The statistical analysis was performed using SYSTAT Version 10 (SPSS Inc., Chicago, IL, USA).

Results

Between January 1993 and December 2012, 1,114 patients with nonmetastatic colorectal cancer underwent elective LCR. Whereas 992 procedures were completed laparoscopically (LAP group), conversion to open surgery was necessary in 122 cases (10.9 %) (CONV group).
The characteristics of the patients are listed in Table 1. The median age was significantly higher in the CONV group than in the LAP group. No differences in gender, body mass index (BMI), ASA score, tumor site, or use of neoadjuvant CRT in rectal cancer patients were observed between the two groups.

Table 1
Baseline patient characteristics

	CONV (n = 122)	**LAP (n = 992)**	**p value**
Gender			
Male n (%)	69 (56.6)	530 (53.4)	0.577
Age years (range)			
Median	68 (47–89)	67 (24–92)	0.018
BMI kg/m^2 (range)			
Median	24 (20–36)	23 (16–47)	0.163
ASA score n (%)			
1	26 (21.3)	184 (18.5)	0.539
2	58 (47.5)	452 (45.6)	0.795
3	37 (30.4)	337 (34)	0.482
4	1 (0.8)	19 (1.9)	0.618
Tumor site n (%)			
Cecum/ascending colon	21 (17.2)	147 (14.8)	0.573
Hepatic flexure	4 (3.3)	33 (3.3)	0.810
Transverse colon	5 (4.1)	28 (2.8)	0.616
Splenic flexure	6 (4.9)	25 (2.5)	0.219
Descending colon	8 (6.6)	58 (5.9)	0.912
Sigmoid colon	33 (27)	350 (35.3)	0.088
Rectum	45 (36.9)	351 (35.4)	0.821
Upper	14 (31.1)	131 (37.3)	0.516
Mid/lower	31 (68.9)	220 (62.7)	
Neoadjuvant CRT n (%)	8(25.8)	66 (30)	0.788

CONV converted, LAP laparoscopically completed, BMI body mass index, ASA American Society of Anesthesiologists, CRT chemoradiation therapy for mid/lower rectal cancer

Intraoperative results

The type of procedure performed was similar in the groups, as reported in Table 2. Among the 122 conversions to open surgery, 59 (48.4 %) were due to a locally advanced cancer, whereas 5 (4.1 %) were due to intraoperative complications (Table 2). No differences were observed in terms of conversion rate between colon and rectal resections (10.7 vs 11.4 %; p = 0.821). The conversion rate did not change significantly over time, as shown in Fig. 1.

Table 2

Perioperative results

	CONV (n = 122)	LAP (n = 992)	p value
Procedure n (%)			
Right hemicolectomy	27 (22.1)	204 (20.6)	0.776
Left hemicolectomy	27 (22.1)	193 (19.4)	0.562
Sigmoidectomy	20 (16.4)	196 (19.8)	0.444
Anterior resection	36 (29.5)	337 (34)	0.377
APR	9 (7.4)	55 (5.5)	0.539
Hartmann	3 (2.5)	7 (0.7)	0.153
Median operative time min (range)			
Overall	180 (90–420)	140 (45–360)	<0.001
Colon	150 (90–330)	125 (45–300)	<0.001
Rectum	200 (130–420)	175 (60–360)	<0.001
Median intraoperative blood loss ml (range)			
Overall	150 (25–1000)	100 (10–2800)	<0.001
Colon	100 (25–1000)	70 (10–600)	<0.001
Rectum	150 (50–1000)	100 (10–2800)	<0.001
Reasons for conversion n (%)			
Tumor related (locally advanced tumor)			
Overall	59 (48.4)		
Colon	44 (57.1)		
Rectum	15 (33.3)		
Non–tumor related			
Overall	63 (51.6)		
Colon	33 (42.9)		
Rectum	30 (66.7)		
Obesity	23 (18.8)		
Adhesions	18 (14.8)		
Subocclusion	11 (9)		
Unclear anatomy	6 (4.9)		
Intraoperative complications	5 (4.1)		
Hypercapnia	2		
Bleeding	2		
Visceral injury	1		
Postoperative complications n (%)			
Overall	20 (16.4)	156 (15.7)	0.849
Colon	10 (12.9)	93 (14.5)	0.864
Rectum	10 (22.2)	63 (17.9)	0.539
Grade 1	3 (2.5)	21 (2.1)	0.806
Grade 2	11 (9.0)	66 (6.7)	0.332
Grade 3	5 (4.1)	63 (6.3)	0.327
Grade 3a	1 (0.8)	12 (1.2)	0.705
Grade 3b	4 (3.3)	51 (5.1)	0.370
Grade 4	0	3 (0.3)	0.543
Grade 5	1 (0.8)	3 (0.3)	0.367

CONV converted, LAP laparoscopically completed, APR abdominoperineal resection

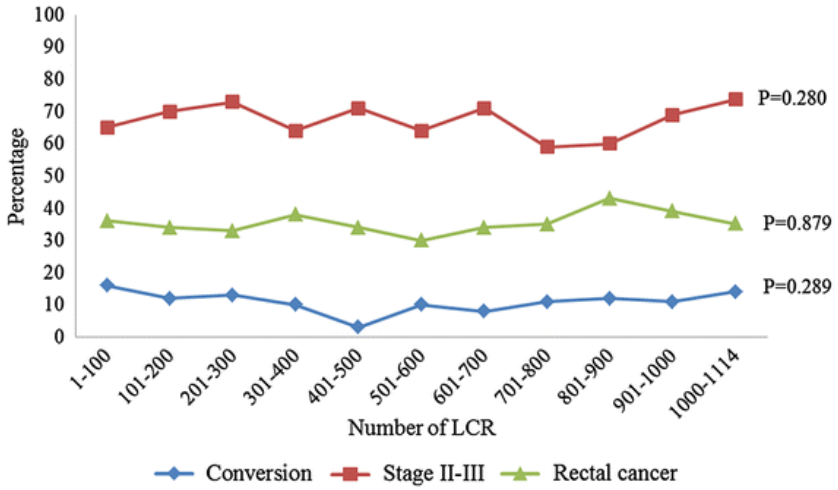

Fig. 1

Conversion, locally advanced cancer, and rectal cancer rates over time. LCR laparoscopic colorectal resection

Overall, the median operative time decreased significantly after the first 100 cases, from 180 min (range, 70–360 min) to 150 min (range, 85–330 min) ($p = 0.049$). We then observed a slow and progressive further reduction in the median operative time to 125 min (range, 45–360 min) in the last 100 cases. The median operative time was 180 min (range, 90–420 min) in the CONV group and 140 min (range, 45–360 min) in the LAP group ($p < 0.001$). The median estimated blood loss was 150 ml (range, 25–1,000 ml) in the CONV group and 100 ml (range, 10–2,800 ml) in the LAP group ($p < 0.001$).

An en bloc multivisceral resection was necessary for five (4.1 %) CONV patients (2 ileal resections, 2 partial cystectomies, and 1 abdominal wall resection) and for 5 (0.5 %) LAP patients (2 ileal resections, 2 distal splenopancreatectomies, and 1 vaginal posterior wall resection).

Short-term postoperative results

Return of bowel function occurred 1 day later in the CONV colon cancer group than in LAP colon cancer group (5 vs 4 days; $p < 0.001$), whereas no differences between the CONV and LAP rectal cancer patients were observed (4 days in both groups; $p = 0.228$).

A significantly higher rate of perioperative blood transfusions was observed in the CONV group (7.4 vs 3.6 %; $p = 0.047$), with no significant differences between the colon and rectal cancer patients (7.8 % of CONV colon cancer patients vs 6.6 % of CONV rectal cancer patients; $p = 0.981$).

No differences were observed in terms of overall 30-day postoperative morbidity rate between the CONV and LAP groups (16.4 vs 15.7 %; $p = 0.849$) regardless of the tumor location (colon vs rectum). In particular, no statistically significant differences were observed between the groups in terms of rates for wound infection (2.5 vs 0.9 %; $p = 0.117$), cardiopulmonary complications (0.8 vs 2.3 %; $p = 0.282$), anastomotic leakage (3.3 vs 4.9 %; $p = 0.416$), reoperation (3.3 vs 5.1 %; $p = 0.370$), or mortality (0.8 vs 0.3 %; $p = 0.367$) (Table 2).

The median postoperative hospital stay was longer in the CONV group than in the LAP group (9 vs 7 days), although the difference did not reach statistical significance ($p = 0.120$). This trend was observed for both colon cancer (8 vs 7 days; $p = 0.303$) and rectal cancer (10 vs 8 days; $p = 0.337$) patients.

Pathologic results

Length of the specimen, number of harvested lymph nodes, and positive margin rates did not differ between the two groups (Table 3). No tumor was detected macroscopically at the specimen margins. Tumor cells were microscopically found at the specimen margin (R1 resection) in one CONV case (0.8 %) and in five LAP cases (0.5 %) (p = 0.837).

Table 3

Pathologic findings

	CONV (n = 122)	**LAP (n = 992)**	**p value**
Median specimen length cm (range)			
Overall	30 (6–50)	28 (6–55)	0.160
Colon	31 (6–50)	29 (6–50)	0.195
Rectum	28 (15–50)	28 (8–55)	0.157
Positive margins n (%)			
Overall	1 (0.8)	5 (0.5)	0.837
Colon	0	0	1
Rectum	1 (2.2)	5 (1.4)	0.518
Lymph nodes resected median n (range)			
Overall	14 (6–47)	13 (5–69)	0.179
Colon	15 (6–47)	14 (5–39)	0.188
Rectum	14 (5–33)	12 (5–69)	0.135
T			
0	0	9 (0.9)	0.603
1	9 (7.4)	345 (34.8)	<0.001
2	13 (10.6)	155 (15.6)	0.189
3	85 (69.7)	446 (45)	<0.001
4	15 (12.3)	37 (3.7)	<0.001
N			
0	67 (54.9)	679 (68.4)	0.004
1	41 (33.6)	174 (17.6)	<0.001
2	14 (11.5)	139 (14)	0.529
TNM stage n (%)			
pCR			
Overall	0	9 (0.9)	0.603
Colon	0	0	1
Rectum	0	9 (2.6)	0.606
1			
Overall	18 (14.7)	337 (33.9)	<0.001
Colon	10 (12.9)	206 (32.1)	<0.001
Rectum	8 (17.8)	131 (37.3)	0.012
2			
Overall	49 (40.2)	333 (33.6)	0.178
Colon	38 (49.4)	225 (35.1)	0.017
Rectum	11 (24.4)	108 (30.8)	0.490
3			
Overall	55 (45.1)	313 (31.6)	0.004
Colon	29 (37.7)	210 (32.8)	0.443
Rectum	26 (57.8)	103 (29.3)	<0.001

CONV converted, LAP laparoscopically completed, TNM tumor node metastasis, pCR pathologic complete response

Significantly lower rates of pT1 (7.4 vs 34.8 %; p < 0.001) and higher rates of pT3 (69.7 vs 45 %; p < 0.001), pT4 (12.3 vs 3.7 %; p < 0.001), and pN1 (33.6 vs 17.6 %; p < 0.001) carcinomas were reported in the CONV group than in the LAP group. The pT4 cancers included five pT4b (33.3 %) in the CONV group and four pT4b (10.8 %) in the LAP group (p = 0.100). Overall, stage 3 tumors were more frequently observed among the CONV patients (45.1 vs 31.6 %; p = 0.004).

Long-term oncologic results

Between January 1993 and December 2007, 600 patients underwent LCR for nonmetastatic cancer and were considered for oncologic analysis. During a median follow-up period of 120 months (range, 60–180 months), 75 patients (12.5 %) were lost to follow-up evaluation. As a result, 525 patients (53 CONV patients and 472 LAP patients) were included in the analysis.

A total of 25 CONV patients (47.2 %) and 161 LAP patients (34.1 %) had rectal cancer (p = 0.083). The distribution of tumor stages in the two groups of patients was as follows: stage 1 (13.2 %, n = 7 vs 33.7 %, n = 159; p = 0.004), stage 2 (37.7 %, n = 20 vs 33.3 %, n = 157; p = 0.617), and stage 3 (49.1 %, n = 26 vs 33 %, n = 156; p = 0.030). The longitudinal and radial margins were clear in all cases. A total of 30 CONV patients (56.6 %) and 251 LAP patients (53.2 %) received adjuvant chemotherapy (p = 0.742).

Tumor recurrence occurred more frequently in the CONV group (33.9 vs 21.2 %; p = 0.035). The local recurrence rate was 11.3 % in the CONV group (6 patients) and 5.1 % in the LAP group (24 patients) (p = 0.064). Distant metastases developed in 12 CONV patients (22.6 %) and in 76 LAP patients (16.1 %, 1 case of port-site metastasis) (p = 0.244). Combined local and distal recurrence was observed in five LAP patients (1.1 %; p = 0.994).

The median time until recurrence did not differ between the two groups (17 months; range, 3–107 months in the CONV group and 20 months; range, 2–108 months in the LAP group; p = 0.374). Both the 5-year OS and DFS rates were significantly lower for the CONV patients (79.4 vs 87.4 %; p = 0.016; Fig. 2A) than for the LAP patients (65.4 vs 79.6 %; p = 0.013; Fig. 2B). No significant differences were observed in a stage-by-stage comparison between the two groups (Table 4).

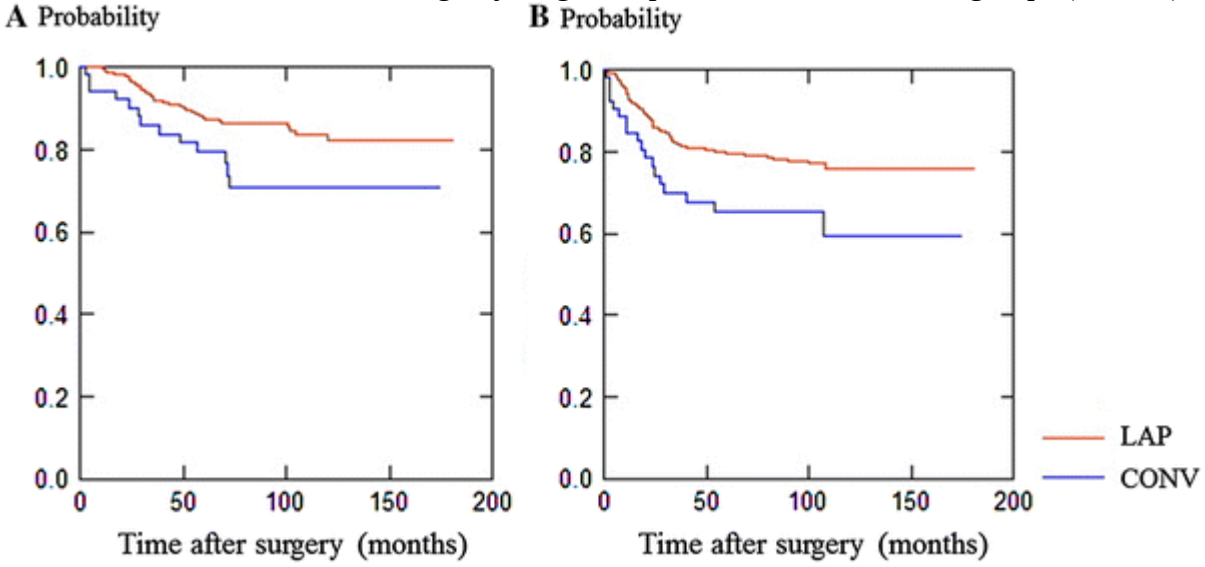

Fig. 2

Long-term oncologic outcomes. A Overall survival (p = 0.016, log-rank test). B Disease-free survival (p = 0.013, log-rank test). LAP laparoscopically completed, CONV converted

Table 4
Oncologic outcomes

	CONV (n = 53) (%)	LAP (n = 472) (%)	p value
5-Year overall survival	79.4	87.4	0.016
Stage 1	100	98.6	0.615
Stage 2	81.3	93	0.112
Stage 3	65.8	70	0.264
5-Year disease-free survival	65.4	79.6	0.013
Stage 1	100	94.2	0.462
Stage 2	74.4	84.7	0.251
Stage 3	49.3	59.3	0.188

CONV converted, LAP laparoscopically completed

The univariate analysis found conversion to open surgery, postoperative complications, anastomotic leakage, pT4 cancer, stage 3 disease (LNR ≥0.01), and adjuvant chemotherapy to be significant risk factors for OS and DFS (Tables 5 and 6). In particular, both the 5-year OS and 5-year DFS were significantly higher for the T1–T3 patients (88.2 vs 51.9 %; $p < 0.001$) than for the pT4 patients (80 vs 38.1 %; $p < 0.001$), and for the stages 1 and 2 patients (95.6 vs 69.3 %; $p < 0.001$) than for the stage 3 patients (88.8 vs 57.9 %; $p < 0.001$).

Table 5
Univariate and multivariate analysis of risk factors for overall survival

	n = 525	Univariate analysis		Multivariate analysis	
		Hazard ratio (95 % CI)	p value[a]	Hazard ratio (95 % CI)	p value[a]
Median age (years)					
>66	256	1			
≤66	269	1.22 (0.75–1.99)	0.428		
Gender					
Female	235	1			
Male	290	0.99 (0.61–1.63)	0.992		
Tumor site					
Colon	339	1		1	
Rectum	186	1.39 (0.85–2.29)	0.185	1.21 (0.64–2.28)	0.559
Conversion to open surgery					
No	472	1		1	
Yes	53	2.07 (1.05–4.08)	0.033	1.01 (0.40–2.49)	0.989
pT staging					
T1–T3	504	1		1	
T4	21	6.18 (2.49–15.29)	<0.001	7.79 (2.47–1.61)	<0.001
No. of harvested lymph nodes					
≥12	291	1			
<12	234	1.09 (0.67–1.77)	0.738		
Lymph node ratio					
0	343	1		1	
0.01–0.24	107	1.62 (0.93–2.83)	0.086	1.46 (0.81–2.52)	0.109
≥0.25	75	8.34 (4.77–14.59)	<0.001	10.03 (4.66–21.59)	<0.001
Perioperative blood transfusion					
No	500	1			
Yes	25	1.48 (0.54–4.08)	0.443		

	n = 525	Univariate analysis		Multivariate analysis	
		Hazard ratio (95 % CI)	p value[a]	Hazard ratio (95 % CI)	p value[a]
Postoperative complications					
No	449	1		1	
Yes	76	1.94 (1.06–3.56)	0.030	1.45 (0.59–3.53)	0.410
Postoperative anastomotic leakage					
No	503	1		1	
Yes	22	2.28 (0.86–6.02)	0.089	1.62 (0.43–6.01)	0.474
Adjuvant CT					
No	244	1		1	
Yes	281	3.95 (2.21–7.06)	<0.001	1.59 (0.79–3.24)	0.194

CI confidence interval, CT chemotherapy
[a]Stepwise logistic regression analysis

Table 6
Univariate and multivariate analysis of risk factors for disease-free survival

	n = 525	Univariate analysis		Multivariate analysis	
		Hazard ratio (95 % CI)	p value[a]	Hazard ratio (95 % CI)	p value[a]
Median age (years)					
>66	256	1		1	
≤66	269	1.33 (0.88–2.02)	0.171	1.06 (0.63–1.81)	0.815
Gender					
Female	235	1			
Male	290	1.04 (0.69–1.57)	0.863		
Tumor site					
Colon	339	1		1	
Rectum	186	1.47 (0.96–2.23)	0.073	1.22 (0.71–2.09)	0.463
Conversion to open surgery					
No	472	1		1	
Yes	53	1.91 (1.04–3.52)	0.035	1.14 (0.51–2.51)	0.753
pT staging					
T1–T3	504	1		1	
T4	21	7.29 (2.98–17.85)	<0.001	5.18 (1.65–16.28)	0.005
No. of harvested lymph nodes					
≥12	291	1			
<12	234	1.11 (0.74–1.68)	0.613		
Lymph node ratio					
0	343	1		1	
0.01–0.24	107	1.75 (1.09–2.81)	0.027	1.86 (0.98–3.98)	0.059
≥0.25	75	7.21 (4.28–12.17)	<0.001	8.29 (4.23–16.29)	<0.001
Perioperative blood transfusion					
No	500	1			

	n = 525	Univariate analysis		Multivariate analysis	
		Hazard ratio (95 % CI)	p value[a]	Hazard ratio (95 % CI)	p value[a]
Yes	25	1.36 (0.56–3–35)	0.498		
Postoperative Complications					
No	449	1		1	
Yes	76	1.62 (0.94–2.77)	0.079	1.05 (0.46–2–37)	0.909
Postoperative anastomotic leakage					
No	503	1		1	
Yes	22	2.50 (1.04–6.01)	0.034	1.95 (0.57–6.65)	0.285
Adjuvant CT					
No	244	1		1	
Yes	281	3.88 (2.39–6.29)	<0.001	1.48 (0.85–2.92)	0.191

CI confidence interval, CT chemotherapy

[a]Stepwise logistic regression analysis

In the multivariate analysis, pT4 cancer and a LNR of 0.25 or more were the only independent predictors of OS and DFS, whereas a LNR of 0.01 to 0.24 showed a trend that did not reach statistical significance (Tables 5 and 6).

Discussion

The feasibility and safety of LCR for cancer has been demonstrated in several RCTs [*1*–*4*]. However, LCR is a technically demanding procedure that involves bowel mobilization in multiple abdominal quadrants, dissection and ligation of large vessels, and restoration of the intestinal continuity with an anastomosis.

Many variables associated with conversion to open surgery have been described. These variables include patient-specific factors such as high BMI, older age, and high ASA score; disease-specific factors such as T4 cancers; and procedure-specific factors such as rectal versus colon resection and the surgeon's experience [*4*, *26*].

We reported a 10.9 % conversion rate in this series of 1,114 patients undergoing LCR for nonmetastatic colorectal cancer. No differences were noted in terms of conversion rates between the colon and rectal cancer patients (10.7 vs 11.4 %). We found that a locally advanced tumor was the most common reason for conversion to open surgery (57.1 % among the colon cancer patients and 33.3 % among the rectal cancer patients), followed by obesity (18.8 %) and adhesions (14.8 %), confirming the data previously reported in the CLASICC trial [*3*].

Currently, we consider a preoperatively suspected T4 colorectal cancer to be a contraindication to LCR. However, 52 patients in our series had a postoperative diagnosis of a pT4 cancer (9 pT4b), reflecting that CT scan sensitivity for the preoperative diagnosis of T4 colorectal cancer is suboptimal [*27*].

Some studies have investigated the learning curve in LCR [*3*, *14*, *28*–*33*], observing the trend in operative time and conversion rate according to the surgeon's experience. For instance, Marusch et al. [*29*] showed a significantly lower conversion rate for surgeons with experience of more than 100 LCRs than for surgeons who had performed fewer than 100 such procedures. In contrast, other studies [*34*] and the current series did not observe significant differences in terms of conversion rate according to the surgeon's experience.

To the best of our knowledge, this study involved the largest series of patients undergoing LCR for nonmetastatic colorectal cancer. We demonstrated a significant decrease in the operative time after the first 100 cases, but no significant differences were observed over time in terms of conversion

rate. This may be related to the fact that in our experience, the learning curve is reflected in the operative time required to complete the procedure, whereas the selection criteria for LCR did not change during the study period (Fig. 1).

Several studies have investigated the impact that conversion of LCR has on perioperative outcomes. The intraoperative results in our series are consistent with those reported in the literature, with conversion to open surgery leading to a significantly longer operative time and increased blood loss [3, 13–18].

Regarding postoperative short-term outcomes, significantly higher morbidity and mortality rates and a prolonged hospital stay are widely reported after conversion of LCR [14, 18, 29, 35, 36]. However, the interpretation of these results is limited by the small and heterogeneous groups of patients considered because many studies have included benign diseases such as diverticulitis and inflammatory bowel disease besides colorectal cancers. Data restricted to cancer patients are more controversial [3, 17, 19, 20, 22]. Whereas some authors [3, 17] have observed that patients undergoing conversion had significantly higher rates of blood transfusions, surgical complications including anastomotic leakage, and reintervention than patients who had a completed LCR, others did not find adverse effects of conversion on the early postoperative outcomes for patients with colorectal cancer.

Franko et al. [19] compared 31 patients undergoing converted LCR with 143 patients undergoing completed LCR. The rates for postoperative morbidity including wound infection, prolonged ileus and anastomotic leaks, in-hospital mortality, and readmission were similar in the two groups. Similar results were reported by Ptok et al. [20] <C>, who did not observe significant differences in terms of morbidity and mortality rates between 56 patients who had conversion and 290 patients who had completed LCR.

In our series, we observed a significantly higher rate of perioperative blood transfusions in the CONV group patient than in the LAP group (7.4 vs 3.6 %; p = 0.047), with no significant difference between the colon and rectal cancer patients (7.8 % of the CONV colon cancer patients vs 6.6 % of the CONV rectal cancer patients). However, there were no statistically significant differences between the CONV and LAP groups in terms of overall postoperative morbidity (16.4 vs 15.7 %) regardless of tumor location, wound infections (2.5 vs 0.9 %), cardiopulmonary complications (0.8 vs 2.3 %), or mortality (0.8 vs 0.3 %). The hospital stay was prolonged in the CONV group (colon cancer patients: 8 vs 7 days; rectal cancer patients: 10 vs 8 days), consistent with the results reported in the literature, although these differences did not reach statistical significance.

In nonrandomized comparative and descriptive studies, conversion also is associated with worse oncologic outcomes in terms of higher local recurrence and reduced survival rates [13, 16, 18, 20, 21, 23]. However, the cited studies present several shortcomings including small sample sizes, short follow-up periods, and lack of adequate statistical analysis that limit the interpretation of the results. To the best of our knowledge, the CLASICC trial is the only RCT that has reported long-term oncologic outcomes for converted patients, whereas all other RCTs have analyzed converted patients in the laparoscopic group on an “intention-to-treat” basis.

Green et al. [10] recently found that converted colon cancer patients had significantly worse OS and DFS, even after adjustment for stratification factors, age, sex, and TNM stage, during a median follow-up period of 62.9 months than patients undergoing open surgery, suggesting that the disease itself adversely affects survival rather than conversion per se.

We analyzed 525 (53 converted) patients with a median follow-up period of 120 months after LCR. The median time until recurrence did not differ between the two groups: 17 months (range, 3–107 months) in the CONV group and 20 months (range, 2–108 months) in the LAP group (p = 0.374). Both OS and DFS were significantly lower for the converted patients. However, in the multivariate analysis, pT4 cancer and a LNR of 0.25 or more were the only independent predictors for DFS and OS, whereas a LNR of 0.01–0.24 showed a trend that did not reach statistical significance. In particular, both 5-year OS and 5-year DFS were significantly poorer for pT4 patients (51.9 vs 88.2 %; p < 0.001) than for pT1–pT3 patients (38.1 vs 80 %; p < 0.001).

We believe that the good results reported in our series of CONV patients are associated with our attitude of considering early conversion for locally advanced colorectal malignancies. This surgical strategy avoids excessive tumor handling or incorrect oncologic dissection by the laparoscopic approach, thus reducing the risk of tumor cell spillage and potentially adverse oncologic outcomes.
Recently, some retrospective studies have specifically investigated oncologic outcomes in T4 colorectal cancer patients after laparoscopic resection [*37*–*39*], concluding that a laparoscopic approach to T4 colorectal cancer is safe and does not affect oncologic outcomes compared with the open approach. However, RCTs are needed to confirm these suggestions.
In conclusion, despite the limitations of a retrospective study, the results of this large series show that locally advanced cancer is the first reason for conversion to open surgery and that a pT4 cancer is independently associated with poor survival. Conversion per se does not adversely affect short-term outcomes or long-term survival in patients with nonmetastatic colorectal cancer.

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